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Patents
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Bassil Dahiyat et al.		
Appln. No.	:	10/082,671	**Conf. No.:**	**8367**
Filed	:	February 22, 2002		
Title	:	USE OF NUCLEIC ACID LIBRARIES TO CREATE TOXICOLOGICAL PROFILES		
Group Art Unit	:	1645		
Examiner	:	Not Yet Assigned		

May 17, 2002
New York, New York

Commissioner for Patents
Washington, DC 20231

PRELIMINARY AMENDMENT

Prior to examining this application, kindly amend the application as indicated below. An Appendix specifying the amendments is attached hereto.

In the Specification:

At page 34, replace the last paragraph with the following:

--In a preferred embodiment, the targeting sequence is a nuclear localization signal (NLS). NLSs are generally short, positively charged (basic) domains that serve to direct the entire protein in which they occur to the cell's nucleus. Numerous NLS amino acid sequences have been reported including single basic NLS's such as that of the SV40 (monkey virus) large T Antigen (Pro Lys Lys Lys Arg Lys Val) (SEQ ID

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NO:56), Kalderon (1984), et al., Cell, 39:499-509; the human retinoic acid receptor-ß nuclear localization signal; NFkB p50 (see, for example, Ghosh et al., Cell 62:1019 (1990)); NFkB p65 (see, for example, Nolan et al., Cell 64:961 (1991)); and others (see, for example, Boulikas, J. Cell. Biochem. 55(1):32-58 (1994), hereby incorporated by reference) and double basic NLS's exemplified by that of the Xenopus (African clawed toad) protein, nucleoplasmin (see, for example, Dingwall, et al., Cell, 30:449-458, 1982 and Dingwall, et al., J. Cell Biol., 107:641-849; 1988).--

At page 37, replace the third full paragraph with the following:

--In a preferred embodiment, the targeting sequence is a lysozomal targeting sequence, including, for example, a lysosomal degradation sequence such as Lamp-2 (KFERQ (SEQ ID NO:57); Dice, Ann. N.Y. Acad. Sci. 674:58 (1992); or lysosomal membrane sequences from Lamp-1 (see, for example, Uthayakumar et al., Cell. Mol. Biol. Res. 41:405 (1995)) or Lamp-2 (see, for example, Konecki et la., Biochem. Biophys. Res. Comm. 205:1-5 (1994)).--

Replace the paragraph bridging pp. 39-40 with the following:

--In a preferred embodiment, the fusion partner is a stability sequence to confer stability to the candidate protein or the nucleic acid encoding it. Thus, for example, peptides can be stabilized by the incorporation of glycines after the initiation methionine, for protection of the peptide to ubiquitination as per Varshavsky's N-End Rule, thus conferring long half-life in the cytoplasm. Similarly, two prolines at the C-terminus impart peptides that are largely resistant to carboxypeptidase action. The presence of two glycines prior to the prolines impart both flexibility and prevent structure initiating events in the di-proline to be propagated into the candidate protein structure.

Thus, preferred stability sequences are as follows: $MG(X)_nGGPP$ (SEQ ID NO:58), where X is any amino acid and n is an integer of at least four.--

REMARKS

Applicants have amended the specification to introduce three references to the sequence listing filed herewith. No new matter is introduced by the amendments.

No fee is believed to be due for the filing of this Preliminary Amendment. However, the Director is authorized to charge any fees that may be due, or to credit overpayment of same, to Deposit Account No. 06-1075.

Respectfully submitted,

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APPENDIX OF AMENDMENTS

At page 34, line 25, before ", Kalderon" insert –(SEQ ID NO:56)–.

At page 37, line 27, before "; Dice" insert –(SEQ ID NO:57)–.

At page 40, line 3, before ", where" insert –(SEQ ID NO:58)–.